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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CHEN, STACY BROWN	
ART UNIT	**PAPER NUMBER**
1648	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/509,302	ZHOU ET AL.	
	Examiner	Art Unit	
	Stacy B. Chen	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-7,10-16,18-22,25-30 and 47-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-7,10-16,18-22,25-30 and 47-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/27/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 27, 2007 has been entered. Claims 1, 3-7, 10-16, 18-22, 25-30 and 47-49 are pending and under examination.

Response to Amendment

2. The rejection of claims 3-5, 10-15, 17-20 and 25-30 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention because the claims contain the trademark/trade name Pluronic® F-68, is either moot in view of a cancelled claim, or withdrawn in view of Applicant's amendment removing the term "Pluronic®F-68".

Specification

3. (*New Objection*) The amendment filed August 27, 2007 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The paragraph beginning on page 4, line 30 of the substitute specification newly recites, "and has an average

molecular weight of 8400 Da." This limitation attempts to define Pluronic® F-68, however, the molecular weight of Pluronic® F-68 was not disclosed in the specification as originally filed. Applicant is required to cancel the new matter in the reply to this Office Action.

Claims Summary

4. The claims as amended are drawn to a method of large-scale virus production, specifically, adenovirus production. The method steps are:

a. Inoculate a cell growth medium with a population of mammalian host cells, wherein the medium contains a shear-protective compound, wherein the shear-protective compound is a block copolymer surfactant;

b. Culture the host cells;

c. Infect the host cells with an aliquot of a virus seed stock essentially free of any cell-lysing component;

d. Culture the virus-infected host cells under gas sparging;

e. Harvest intracellular and extracellular virus from the host cells and medium; and,

f. Purify the harvested virus.

Specifically, the shear-protective compound is a polyoxyethylene-polyoxyprophylene block copolymer having an average molecular weight of 8400 Da, in a concentration from about 0.3 g/L to about 10 g/L, more specifically, 1 g/L to about 2 g/L. During the virus production method, gas sparging is provided at a rate up to about 0.1 VVM, or more specifically, a rate up to about 0.001 to 0.05 VVM. Adenoviruses are grown in PER.C6® cells. PER.C6® are known and publicly available at the ECACC, deposit number 96022940. The cell-lysing component referred to in step c) of the method is present at a concentration less than 0.00025%.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

(*New Rejection*) Claims 3-5, 10-15, 18-20, 25-30, 48 and 49 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection. There are two aspects to this rejection:

a) Claims 3-5, 10-15, 18-20 and 25-30 recite the limitation, "polyoxyethylene-polyoxyprophylene block copolymer having an average molecular weight of 8400 Da". The Office considers the language "polyoxyethylene-polyoxyprophylene block copolymer", to be supported by the specification, however, the inclusion of a molecular weight of 8400 Da does not appear to be supported by the specification as originally filed. Applicant points to several non-patent literature references that refer to Pluronic®F-68 as having an average molecular weight of 8400 Da, as well as the MPEP 608.01(v) and 2163.

The Office notes that Pluronic®F-68 is available in several different forms, all of which are 8400 Da, with the exception of Pluronic®F-68 LF Pastille, which has a molecular weight of 7500 Da (see attached BASF Pluronic® data sheet). It is unclear whether Applicant, at the time of filing, meant to encompass Pluronic®F-68 as a genus (which would include the 8400 Da and

7500 Da forms available), or Pluronic®F-68 itself (not including any other forms such as Pastille, LF Pastille, NF Prill Poloxamer 188, and Prill). Deletion of the molecular weight in question would overcome this aspect of the rejection.

b) Claims 48 and 49 recite, "wherein the cell-lysing component is present at a concentration less than 0.00025%". Applicant points to the specification, page 9, lines 25-33, page 13, lines 25-26, and page 29, lines 5-8. The particular portion that Applicant appears to rely on is page 29, lines 5-8, reproduced below:

> ***Experiment 4 - Effect of buffer A containing 1% PS-80 on virus production in sparged cultures*** **- For all previous experiments in this Example conducted at the 2L and roller bottle scale, the virus seed used was formulated in Buffer A (which includes 1% PS-80). Upon addition to the reactor, this amounts to a final concentration of the buffer A in the culture of 0.025% v/v.**

Applicant asserts that PS-80 (the cell-lysing component) is 1% of a 0.25% final concentration of buffer A. The Office notes that the final concentration of the buffer A in the culture is 0.025% v/v. It appears that the claimed concentration of 0.00025% was calculated by taking 1% of 0.025%. Applicant is requested to confirm that this is the derivation of the instantly claimed concentration of 0.00025%. If this is the case, then the Office considers the PS-80 concentration of 0.00025% to be adequately described. However, note that the claims recite, "at a concentration less than 0.00025%". The specification does not adequately provide for "less than 0.00025%", and may, at best, only provide for PS-80 at 0.00025% exactly. The other text in the specification that discusses "essentially free of any cell-lysing component" does not define a number or describe the limitation in claims 48 and 49.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3-7, 10-16, 18-22, 25-30 and 47-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jianyong Wu (*Journal of Biotechnology*, 1995, 43:81-94, "Wu"), in view of Brough *et al.* (US Patent 6,113,913, "Brough"), and Murhammer *et al.* (*Bio/Technology*, December 1998, 6:1411-1418, "Murhammer"). The claims are summarized above.

Wu discloses that the industrial application of animal cell cultures for production of biologicals (viral vaccines and other products) requires large-scale cell culture processes, processes that are posed with challenges such as oxygen supply (page 81). Wu teaches that suspension cultures that use sparging aeration can lead to animal cell death (page 81-82, bridging paragraph). Wu discloses that protective medium additives can protect animal cells, such as FBS, Pluronic® F-68, and methylcellulose (page 82, first column, last paragraph). Wu does not disclose the production of adenoviruses, PER.C6® cells, or the particular concentrations of Pluronic® F-68.

However, Brough discloses that recombinant adenoviruses (E1 deficient) are highly desirable vehicles for gene delivery and transfer (col. 1, lines 9-27) that are produced in PER.C6® cells, which express adenovirus E1 helper function (col. 9, lines 43-45).

Murhammer discloses the scaleup (large-scale production) of insect cell cultures using Pluronic® F-68 as a protective agent against cell lysis (abstract). Murhammer extended the

study to include the scaleup of insect cell cultures infected with baculovirus comprising a gene encoding β-galactosidase. The following method steps are disclosed in the reference:

- Sf9 insect cells were cultured in spinner flasks to provide cells for seeding the spinner flasks and bioreactors (page 1414, last paragraph). TNM-FH medium was supplemented with gentamycin sulfate, Fungizone, heat-inactivated FBS, various concentrations of Pluronic® F-68 (0.2%) and an antifoam compound (see Table 2). Murhammer discloses that although 0.2% Pluronic® F-68 provided full protection from sparging during growth phrase, a higher concentration of Pluronic® F-68 may be required in order to fully protect virally-infected cells (page 1414, first full paragraph).
- Cells were infected with an AcNPV vector containing the *E. coli* β-galactosidase gene (page 1414, last paragraph).
- Infected cells were cultured in a 3-liter water-jacketed bioreactor with a sparger of 7 holes (page 1418, first column, third full paragraph). The sparged reactor was operated at 200 rpm. β-galactosidase synthesis and extracellular virus per 10^6 virally-infected cells in sparged and unsparged systems was measured (Table 2 and page 1418, first column, last paragraph, "Quantitation of virus and β-galactosidase activity").
- The extracellular virus was quantified by collecting the supernatant after centrifuging the cell-virus suspension.
- Murhammer quantified virus titers in PFUs/ml using the $TCID_{50}$ method.

It would have been obvious to perform the scale-up of mammalian cell culture for the production of adenovirus vectors using Pluronic® F-68. One would have been motivated to propagate adenoviral vectors on a large scale because of their usefulness as gene delivery vehicles (Brough, col. 1, lines 9-27). One would have been motivated to use Pluronic® F-68 in the large scale method because Wu discloses that Pluronic® F-68 is a protective medium additive that can protect animal cells during gas sparging (Wu, page 82, first column, last paragraph). One would have had a reasonable expectation of success that Pluronic® F-68 would have had a protective effect on animal cells infected with adenovirus during gas sparging because Murhammer teaches the propagation of insect cells on a large scale using Pluronic® F-68. On page 1411, top of second column, Murhammer discloses that "Several polymers have been identified which provide protection to mammalian cells in a sparged environment, including the surfactant Pluronic® F-68, which is usually used at a concentration of 0.1% (w/v) or less". Murhammer also discloses that there are "many examples of growing mammalian cells

in small-scale, sparged cultures using medium supplemented with Pluronic® F-68", page 1411, second column, first complete paragraph. Given these teachings, one would have known that Pluronic® F-68 is known to protect mammalian cells against gas sparging in small-scale cultures. It is this knowledge that Murhammer uses to derive the scale-up of insect cells with Pluronic® F-68. One would have had a *reasonable* expectation of success that the scale-up of mammalian cell cultures that use gas sparging would be successful in view of the fact that Pluronic® F-68 is disclosed as protective of mammalian cells.

With regard to the limitation regarding virus seed being essentially free of any cell-lysing component, and new claims 48 and 49 (the specific concentration of cell-lysing component being less than 0.00025%), these embodiments are not considered to lend a patentable distinction over the prior art. It would have been well within the ability of one of ordinary skill in the art to adjust the amount of cell-lysing component concentration for achieving the optimum virus productivity. It would have been obvious to minimize the amount of cell-lysing component in the virus seed stock in order to minimize cell lysis when virus production is initiated with the virus seed stock, yielding a predictable result of reduced cell lysis during virus propagation. Therefore, the invention as a whole would have been obvious to one of ordinary skill in the art at the time the instant invention was made.

Applicant's arguments have been carefully considered but fail to persuade. Applicant's substantive arguments are primarily directed to the following:

- Applicant argues that there is no suggestion or motivation to combine Wu, Brough and Murhammer, given all the teachings of the prior art. Particularly, Applicant argues that the rejection only cites the portions of Murhammer's teachings that relate

to growth of uninfected cells, as opposed to the instant invention, virally infected cells. Applicant notes that little is known about the shear-sensitivity of infected mammalian cell cultures (specification, page 5, lines 9-15). Applicant argues that Murhammer observed very little cell growth and a significant drop in cell viability after infection with virus, which casts doubt on the usefulness of Pluronic®F-68 in virus production. Applicant also points out that increasing the concentration of Pluronic®F-68 failed to fully protect virally-infected cells from lysis. Applicant argues that when considering the prior art as a whole, Pluronic®F-68 has been shown to have a significant negative impact on virus production (Palomores *et al.*, 2000).

- In response to Applicant's arguments, as outlined in the rejection above, Wu suggests the use of Pluronic®F-68 in cell culture for the production of biologicals, including viruses. The particular concentration of Pluronic®F-68 is taught by Murhammer, though in the context of insect cells. The express suggestion of Wu is the motivation to use Pluronic®F-68 in mammalian cell culture for the production of viruses. Determining the particular concentration of Pluronic®F-68 is within the ability of the ordinary artisan. Murhammer's teachings suggest concentrations of Pluronic®F-68 in the context of insect cells for virus production, which reasonably serves as a baseline for determining the optimal concentration for virus production in mammalian. The Office recognizes that Murhammer's results with insect cells for virus production are not considered by Applicant to be adequate to obviate the claimed invention. Note however, that the claims do not require any particular level of virus production.

- Applicant argues that, with respect to the use of virus seed stocks essentially free of any cell-lysing component, there is no basis for applying the teachings of baculovirus production in insect cells to the large-scale production of virus in mammalian cells. Applicant notes that baculovirus production and harvesting in insect cells does not require cell-lysing components, as opposed to mammalian cells (Xie *et al.*, 2003). Applicant further asserts that it was unexpected that the presence of a cell-lysing component (PS-80) at a concentration of 0.00025% would have such an impact on virus production.
  - In response to Applicant's argument, the limitation regarding virus seed being essentially free of any cell-lysing component, and the embodiments of new claims 48 and 49 (the specific concentration of cell-lysing component being less than 0.00025%) are not considered to be a patentable distinction over the prior art. It would have been well within the ability of one of ordinary skill in the art to adjust the amount of cell-lysing component concentration for achieving the optimum virus productivity. It would have been obvious to minimize the amount of cell-lysing component in the virus seed stock in order to minimize cell lysis when virus production is initiated with the virus seed stock, yielding a predictable result of reduced cell lysis during virus propagation.
  - Further, the unexpected results referred to by Applicant in Xie *et al.*, (*Biotechnology and Bioengineering*, 83(1):45-52, July 5, 2003) were published by another after the effective U.S. filing date of the instant application. It does not appear that Applicant appreciated this particular concentration of PS-80 as

yielding unexpected results, although the specification may disclose the exact amount. Applicant is requested to point out the unexpected results disclosed in the specification.

Conclusion

7. No claim is allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Stacy B. Chen/ 9-24-2007
Primary Examiner, TC1600